

## Remarks

This paper is responsive to the Office Action mailed December 1, 2010. This paper is filed with a request for a one-month extension of time. Claims 1-8, 12-19, and 23-31 are pending in the instant application. In the Action, the Office rejected claims 1-8, 12-19, and 23-31. Applicant hereby amends claims 1 and 13. The amendments are fully supported by the application as filed.

### Rejection – 35 U.S.C. § 112

The Office has rejected claims 1-6, 8, 12-17, 19, and 23 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. The Office states that the omitted elements are “the step of filtering out any undissolved particles, originally recited as step (c).” The Office further states that “[i]t is known in the art that undissolved particles can interfere and prevent crystallization of the desired product.” Office Action of December 1, 2010, page 3. Applicant respectfully traverses the rejection.

Applicant respectfully submits that although it is known in some instances in the art that filtration is beneficial as stated in Ault (Techniques and Experiments for Organic Chemistry, 1987, pages 44-46), it is also recognized in the art that filtration is not a requirement for successful crystallization. In fact, in some crystallizations seed crystals are added to accelerate the rate of or induce crystallization. In these cases, seed crystals or small amounts of particulate matter may serve as nucleation sights for crystal growth. Further, Advanced Practical Organic Chemistry (Leonard, Lygo, and Procter, 1995, page 185, paragraph 3 titled *Filter the hot solution to remove insoluble impurities*) states “[t]his step is often problematic and should NOT be carried out unless an unacceptable (use your judgment) amount of insoluble material is suspended in the solution.” Hence, it is understood by one of ordinary skill in the art that filtration is NOT a requirement for successful crystallization. Applicant respectfully submits that for at least these reasons, the instant claims are not missing essential elements, and respectfully requests withdrawal of the rejection.

Rejection – 35 U.S.C. § 103(a)

The Office has rejected claims 1-8, 12-19, and 23-31 under 35 U.S.C. § 103(a) as being unpatentable over Faraq *et al.* (Bull. Pharm. Sci. Assiut University, 1998, 21(1), 1-6) and Feldman *et al.* (Phytochemistry, 1999, 51, 867-872), in view of Pfeffer *et al.* (U.S. Patent No. 4,107,425), Experimental Organic Reactions (1957, 18, pages 504-504), and Ault (Techniques and Experiments for Organic Chemistry, 1987, pages 44-46 and pages 120-121). The Office states that “[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to separate the alpha and beta anomers of penta-O-galloyl-D-glucose from a mixture of the alpha and beta anomers via the method as instantly claimed since analogous separations of the alpha and beta anomers of glucose derivative [*sic*] structurally similar to pentagalloyl glucose via crystallization using water/methanol or acetone as solvents have been disclosed in the prior art.” Office Action of December 1, 2010, page 7. Applicant respectfully traverses the rejection.

Applicant respectfully submits that Faraq discloses the chromatographic separation of alpha and beta PGG mixtures. The method chosen by Faraq to purify the materials is reverse phase high performance liquid chromatography (HPLC), an expensive and more time consuming method than crystallization. Faraq states that “[r]epeated ODS column chromatography and further purification on MCI-gel CHP-20P of the EtOAc soluble fraction...” was required to obtain 19mg of beta PPG starting from approximately 5g of the EtOAc soluble fraction. Faraq did not choose crystallization as a method to purify the crude mixtures or the semi-pure gels in route to obtain the solid compounds described as in the manuscript as “white amorphous powders” even though the Office asserts that crystallization would have been an obvious choice to a person having ordinary skill in the art.

The Office also asserts “that there is a difference in solubility of the alpha and beta anomers of PGG in water and this can be taken advantage of for separation of two anomers from solution containing a mixture of the two anomers in water.” Faraq does not comment of the solubility of the two PGG anomers, and it is known in the art that HPLC separates compounds based upon differences in affinity or size, not solubility. Furthermore, Faraq does not teach that

PGG anomers can be separated based upon differences in solubility (*i.e.*, via an extraction) or by crystallization, therefore one of ordinary skill in the art would not reasonably expect the claimed compounds to crystallize based on the disclosure of Faraq.

Applicant respectfully submits that Feldman discloses the chromatographic separation of benzylated derivatives of alpha and beta PGG mixtures. Benzylated derivatives of PGG possess dramatically different properties than the non-benzylated PGG anomers. For example, the molecular weight of the benzylated derivatives is 1783 g/mol, while the molecular weight of the claim compounds is 941 g/mol. Furthermore, the benzylated compounds are relatively non-polar compounds, while alpha and beta PGG are highly polar because of multiple free hydroxyl groups (*e.g.*, 15 free hydroxyl groups in total). Applicant submits that for at least these reasons the separation of alpha and beta PGG by Faraq and benzylated PGG-derivatives by Feldman would not be obvious to one of ordinary skill in the art as an indication that the separation of alpha and beta PGG as claimed is possible by methods other than reverse phase HPLC.

Applicant respectfully submits that Pfeffer discloses the crystallization of a tetra benzylated sugar, containing no free hydroxyl groups. As previously discussed, benzylated derivatives are chemically different from sugars containing free hydroxyl groups in respect to solubility, polarity, and molecular mass. Pfeffer was able to crystallize the beta anomer of tetra-O-benzyl-1-hexadecanoyl-D-glucose which contains no free hydroxyl groups, whereas beta PGG contains a total of 15 free hydroxyl groups. In addition, Pfeffer teaches that not all glucose derivatives can be crystallized (Table 1, entries 1-3, superscript b (noncrystallizable glasses)). Pfeffer teaches that not all anomers may be separated by crystallization, and even closely related benzylated glucose-derivatives (*e.g.*, tetra-O-1-pentadecanoyl-D-glucose and tetra-O-1-heptadecanoyl-D-glucose; derivatives identical in nature to tetra-O-benzyl-1-hexadecanoyl-D-glucose with the exception of a single -CH<sub>2</sub>- group in the alkyl chain attached at the anomeric position) may behave unpredictably. Since “[a] prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention.” (MPEP 2141.02 VI) Applicant respectfully submits that Pfeffer must be considered in its’ entirety, suggesting that even compounds identical in nature with the exception of a single methylene (*i.e.*, -CH<sub>2</sub>-) group cannot be expected to behave in a predictable manner. Applicant

also submits that for these reasons the separation of benzylated derivatives described by Feldman and Pfeffer would not be obvious to one of ordinary skill in the art as an indication that the significantly more polar, non-benzylated alpha and beta PGG compounds could be separated as claimed is possible.

Applicant respectfully submits that *Experimental Organic Reactions* disclosed the difficulty and uncertainty encountered when crystallization is attempted as a method of purification. Although the Office states that “[a]ccording to *Experimental Organic Reactions* resolution of racemic modification (separation of anomers/optical isomers) can occur via recrystallization,” the authors of *Experimental Organic Reactions* further go on to state that “the success for this method is rare, ... if there are suitable conditions to give a different solubility between a racemic modification and the active substance and thus they can be resolved to some extent.” In addition to the fact that successful crystallization is rare as stated in *Experimental Organic Reactions*, benzylated derivatives (e.g., ethers) as crystallized by Pfeffer possess drastically different chemical and physical properties than polyhydroxylated esters as in the case of PGG. Applicant respectfully submits that one of ordinary skill in the art reading *Experimental Organic Reactions* either individually or together with the other cited references would not find the instant claims to be obvious.

Also, it is instructive that Faraq, Feldman, and Pfeffer do not disclose the use of crystallization to purify alpha or beta PGG, but only benzylated glucose derivatives, which have drastically different chemical and physical properties than polyhydroxylated sugar derivatives. In addition, Ault (*Techniques and Experiments for Organic Chemistry*, 1987, pages 44-46 and 120-121) does not provide any particular insight into why one of ordinary skill would choose crystallization with the claimed solvents to separate the particular claimed compounds. Applicant respectfully submits that one of ordinary skill in the art reading Faraq, Feldman, Pfeffer, *Experimental Organic Reactions*, and Ault either individually or together would not find the instant claims obvious.

As for the articulated reasons as to why the claimed invention would be obvious, Applicant again respectfully disagrees with the Office's assertions. Rationale (A): The Office

asserts that the instant claims combine prior art elements according to known methods to yield predictable results. The results of crystallization attempts of alpha and beta PGG are not predictable. Crystallization is a general method to separate and purify compounds, but far more often than not it cannot be applied because suitable solvents and conditions cannot be found to make compounds crystallize. The crystallization of molecules (especially molecules like PGG) is highly unpredictable, especially when functional groups vary drastically in chemical and physical properties (*e.g.*, ethers as compared to esters or free hydroxyl groups). Rationale (C): The Office asserts that a known technique was used to improve similar devices (methods, or products) in the same way. Applicant respectfully submits that the results of the claimed methods were unexpected because of the previously known tendency of PGG to form gels (rather than crystals) in most solvents in which it dissolves. Rationale (E): The Office asserts that it was obvious to try choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. As previously stated, there is no reasonable expectation of success for crystallization (see Pfeffer; compounds that varied by a single  $-CH_2-$  group failed to crystallize, once again demonstrating the difficulty and low probability of finding general conditions for crystallization), especially when working with larger molecules (*e.g.*, molecular weight > 500 g/mol). In addition, the known high tendency of the PGG to form gels lowers the expectation of success even more. Applicant respectfully submits that for at least these reasons the claimed inventions are not obvious, and respectfully requests withdrawal of the rejection.

In the event the Commissioner should decide that any additional fee or fee deficiency is due, the Commissioner is hereby authorized to charge any and all fees incurred as a result of entering or considering this document to deposit account number 03-0172.

Respectfully submitted,

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